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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Not Yet Assigned
Group : Not Yet Assigned
Applicants : Mundy, Gregory R. and Yoneda,
Toshiyuki
Application No. : Not Yet Assigned
Confirmation No. : Not Yet Assigned
Filed : Concurrently herewith
For : METHODS OF TREATING MULTIPLE
MYELOMA AND MYELOMA-INDUCED BONE
RESORPTION USING INTEGRIN
ANTAGONISTS

New York, New York
February 21, 2002

Hon. Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to examining the above-identified
application, please amend the application as follows.

IN THE CLAIMS

Please amend claim 1 as follows.*

* An "Appendix to Claim Amendment" is enclosed at Tab A,
(continued...)

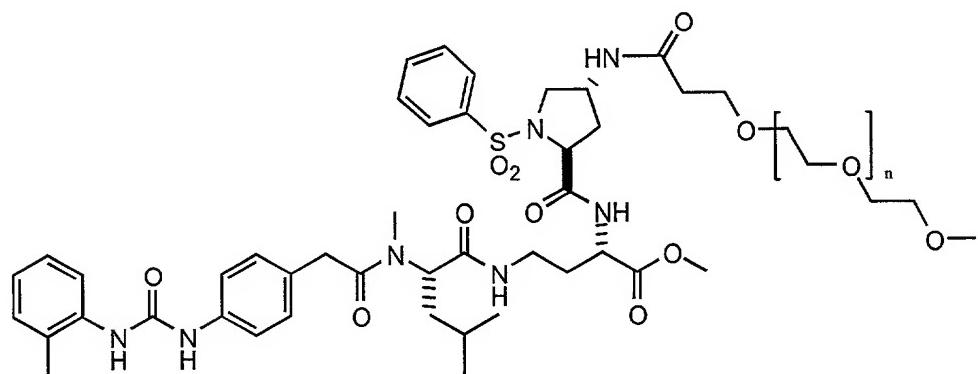
1. (Amended) A method for treating multiple myeloma comprising administering to an individual a therapeutically effective amount of a composition comprising an antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin, wherein said antagonist is a small molecule.

Please cancel claims 2-50 without prejudice.

Please add claims 51-85.

51. (New) The method according to claim 1, wherein said antagonist is an antagonist of VLA-4.

52. (New) The method according to claim 1, wherein said small molecule is:



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* (...continued)
showing the amendments to claim 1. In that Appendix, the added portion of text is underscored.

53. (New) A method for treating multiple myeloma comprising administering to an individual a therapeutically effective amount of a first composition comprising an antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin, wherein said first composition is administered in combination with a therapeutically effective amount of a second composition comprising a compound that is not an antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin.

54. (New) The method according to claim 53, wherein said compound is a chemotherapeutic agent.

55. (New) The method according to claim 53 or claim 54, wherein said antagonist is an anti-VLA4 antibody homolog.

56. (New) A method for treating multiple myeloma comprising administering to an individual a therapeutically effective amount of a first composition comprising an antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin, wherein said first composition is administered in combination with a therapeutically effective amount of a

second composition comprising a compound selected from the group consisting of melphalan, a bisphosphonate, thalidomide, erythropoietin, an antagonist of IL6 and an antagonist of IL15.

57. (New) The method according to claim 56, wherein said compound is melphalan.

58. (New) The method according to claim 56, wherein said antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin is an anti-VLA4 antibody homolog.

59. (New) The method according to claim 53 or claim 56, wherein, to be therapeutically effective, a dosage of said antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin is lower when administered in combination with said second composition than not administered in combination with said second composition; or a dosage of said compound is lower when administered in combination with said first composition than not administered in combination with said first composition; or both.

60. (New) The method according to claim 59,

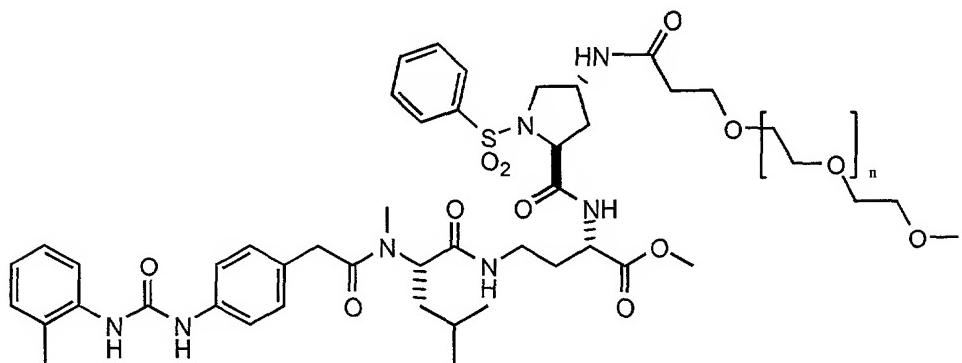
wherein said compound is a chemotherapeutic agent.

61. (New) The method according to claim 59,
wherein said compound is melphalan.

62. (New) A method for inhibiting bone resorption associated with tumors of bone marrow, the method comprising administering to a mammal with said tumors an antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin, in an amount effective to provide inhibition of said bone resorption, wherein the antagonist is a small molecule.

63. (New) The method according to claim 62,
wherein said antagonist is an antagonist of VLA-4.

64. (New) The method according to claim 62,
wherein said small molecule is:



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65. (New) A method for inhibiting bone resorption associated with tumors of bone marrow, the method comprising administering to a mammal with said tumors an antagonist of an interaction between an α_4 subunit-bearing integrin and a ligand for an α_4 subunit-bearing integrin, in an amount effective to provide inhibition of said bone resorption, wherein said antagonist is administered in combination with a compound, in an amount effective to provide inhibition of said bone resorption, that is not an antagonist of an interaction between an α_4 subunit-bearing integrin and a ligand for an α_4 subunit-bearing integrin.

66. (New) The method according to claim 65,
wherein said compound is a chemotherapeutic agent.

67. (New) The method according to claim 65 or
claim 66, wherein said antagonist is an anti-VLA4 antibody
homolog.

68. (New) A method for inhibiting bone resorption associated with tumors of bone marrow, the method comprising administering to a mammal with said tumors an antagonist of an interaction between an α_4 subunit-bearing integrin and a ligand for an α_4 subunit-bearing integrin, in an amount effective to provide inhibition of said bone resorption, wherein said antagonist is administered in

combination with a compound, in an amount effective to provide inhibition of said bone resorption, selected from the group consisting of melphalan, a bisphosphonate, thalidomide, erythropoietin, an antagonist of IL6 and an antagonist of IL15.

69. (New) The method according to claim 68, wherein said compound is melphalan.

70. (New) The method according to claim 68, wherein said antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin is an anti-VLA4 antibody homolog.

71. (New) The method according to claim 65 or claim 68, wherein, to be therapeutically effective, a dosage of said antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin is lower when administered in combination with said compound than not administered in combination with said compound; or
a dosage of said compound is lower when administered in combination with said antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin than not administered in combination with said antagonist of an interaction between

an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin;
or both.

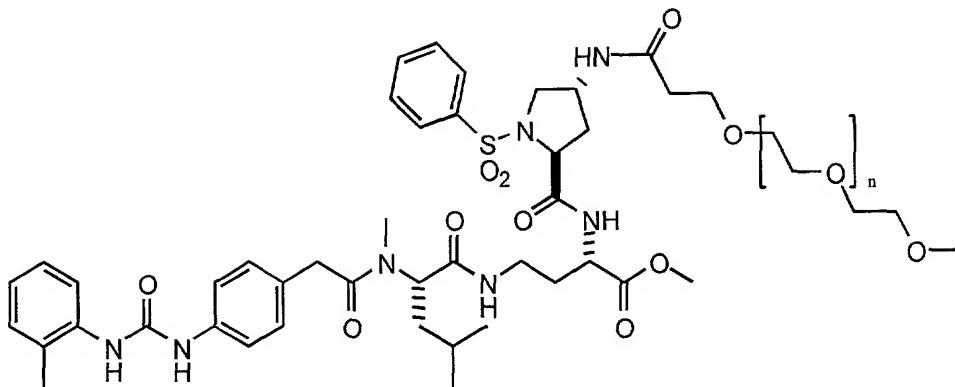
72. (New) The method according to claim 71,
wherein said compound is a chemotherapeutic agent.

73. (New) The method according to claim 71,
wherein said compound is melphalan.

74. (New) A method of treating a subject having
a disorder characterized by the presence of
osteoclastogenesis, the method comprising administering to
the subject an antagonist of an interaction between an $\alpha 4$
subunit-bearing integrin and a ligand for an $\alpha 4$ subunit
bearing integrin, in an amount sufficient to suppress the
osteoclastogenesis, wherein the antagonist is a small
molecule.

75. (New) The method according to claim 74,
wherein said antagonist is an antagonist of VLA-4.

76. (New) The method according to claim 74,
wherein said small molecule is:



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77. (New) A method of treating a subject having a disorder characterized by the presence of osteoclastogenesis, the method comprising administering to the subject an antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit bearing integrin, in an amount sufficient to suppress the osteoclastogenesis, wherein said antagonist is administered in combination with a compound, in an amount sufficient to suppress the osteoclastogenesis, that is not an antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin.

78. (New) The method according to claim 77, wherein said compound is a chemotherapeutic agent.

79. (New) The method according to claim 77 or

claim 78, wherein said antagonist is an anti-VLA4 antibody homolog.

80. (New) A method of treating a subject having a disorder characterized by the presence of osteoclastogenesis, the method comprising administering to the subject an antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit bearing integrin, in an amount sufficient to suppress the osteoclastogenesis, wherein said antagonist is administered in combination with a compound, in an amount sufficient to suppress the osteoclastogenesis, selected from the group consisting of melphalan, a bisphosphonate, thalidomide, erythropoietin, an antagonist of IL6 and an antagonist of IL15.

81. (New) The method according to claim 80, wherein said compound is melphalan.

82. (New) The method according to claim 80, wherein said antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin is an anti-VLA4 antibody homolog.

83. (New) The method according to claim 77 or claim 80, wherein, to be therapeutically effective,

a dosage of said antagonist of an interaction between an α_4 subunit-bearing integrin and a ligand for an α_4 subunit-bearing integrin is lower when administered in combination with said compound than not administered in combination with said compound; or
a dosage of said compound is lower when administered in combination with said antagonist of an interaction between an α_4 subunit-bearing integrin and a ligand for an α_4 subunit-bearing integrin than not administered in combination with said antagonist of an interaction between an α_4 subunit-bearing integrin and a ligand for an α_4 subunit-bearing integrin;
or both.

84. (New) The method according to claim 83,
wherein said compound is a chemotherapeutic agent.

85. (New) The method according to claim 83,
wherein said compound is melphalan.

REMARKS

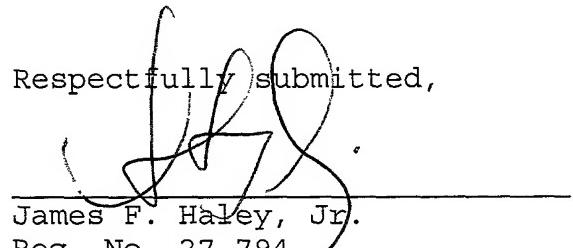
Applicants have canceled claims 2-50 without prejudice. Applicants have amended claim 1 and added claims 51-85 to more particularly point out and distinctly claim applicants' invention. None of the amendments and added claims encompasses new matter. claims 1 and 51-85 are

pending.

Amended claim 1 and added claims 51-85 are clearly supported in the Specification. See, e.g., original claim 1 and claims 2-50. See also, page 50, line 1 to page 55, line 14, page 32, line 23 to page 33, line 16, page 34, line 23 to page 43, line 26 and page 31, lines 12-21.

Applicants request entry of the above amendments and allowance of the pending claims.

Respectfully submitted,



James F. Haley, Jr.
Reg. No. 27,794
Attorney for Applicants
Stanley D. Liang
Reg. No. 43,753
Agent for Applicants
FISH & NEAVE
Customer No. 1473
1251 Avenue of the Americas
New York, New York 10020-1104
Tel.: (212) 596-9000

Appendix to Claim Amendment

1. (Amended) A method for treating multiple myeloma comprising administering to an individual a therapeutically effective amount of a composition comprising an antagonist of an interaction between an $\alpha 4$ subunit-bearing integrin and a ligand for an $\alpha 4$ subunit-bearing integrin, wherein said antagonist is a small molecule.